

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

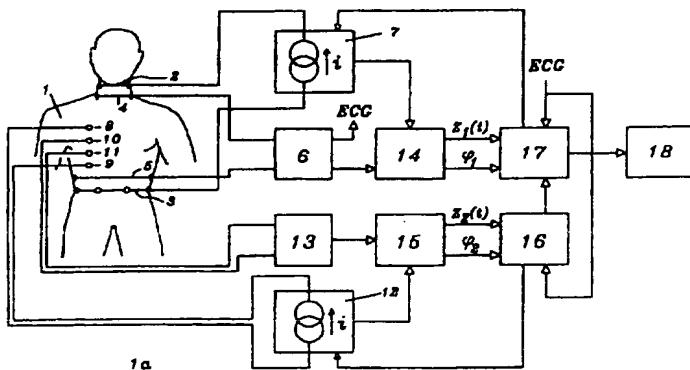


AX

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61B 5/05	A2	(11) International Publication Number: WO 97/11638 (43) International Publication Date: 3 April 1997 (03.04.97)
(21) International Application Number: PCT/NL96/00374		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 25 September 1996 (25.09.96)		
(30) Priority Data: 1001282 26 September 1995 (26.09.95) NL		
(71) Applicant (for all designated States except US): A.J. VAN LIEBERGEN HOLDING B.V. [NL/NL]; Rietspinner 11, NL-3831 DP Leusden (NL).		
(72) Inventors; and		Published
(75) Inventors/Applicants (for US only): HEETHAAR, Robert, Martin [NL/NL]; Willem Alexanderweg 44, NL-3945 CK Cothen (NL). GOOVAERTS, Hendrik, Gebhard [NL/NL]; Bruinjoost 15, NL-1241 HN Kortenhoef (NL).		<i>In English translation (filed in Dutch). Without international search report and to be republished upon receipt of that report.</i>
(74) Agent: VAN BREDA, Jacques; Octrooibureau Los en Stigter B.V., Weteringschans 96, NL-1017 XS Amsterdam (NL).		

(54) Title: APPARATUS FOR THE IN-VIVO NON-INVASIVE MEASUREMENT OF A BIOLOGICAL PARAMETER CONCERNING A BODILY FLUID OF A PERSON OR ANIMAL



(57) Abstract

The invention relates to an apparatus for the in-vivo non-invasive measurement of a biological parameter concerning a bodily fluid of a person or animal in accordance with a calculation model, wherein the apparatus is provided with connections for at least two pairs of electrodes (2-5, 8-11) to be placed on the skin of a part of the body, a pair of input electrodes (2, 3, 8, 9) for feeding a measuring alternating current to the part of the body and a measuring pair of electrodes (4, 5, 10, 11) for measuring the voltage at the measuring pair of electrodes, comprising a current source (7, 12) providing the measuring alternating current, a transformer (31) for the transformation of the measuring voltage into a bio-impedance signal, being a measure of the bio-impedance of the part of the body, and means for the generation of signals which form a measure for further parameters, with the aid of which the parameters to be determined can be determined with the aid of the calculating model, said signals encompassing a signal forming a measure for the time derivative of the bio-impedance signal. The current source (7, 12) has a minimal radiation configuration and is suitable for generating a measuring current having a constant amplitude on at least two frequencies, a low frequency and a high frequency, in a frequency range of up to about 2000 kHz.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

Apparatus for the in-vivo non-invasive measurement of a biological parameter concerning a bodily fluid of a person or animal

The present invention relates to an apparatus for the in-vivo non-invasive measurement of a biological parameter concerning a bodily fluid of a person or animal, wherein the apparatus is provided with at least two pairs 5 of electrodes to be placed on the skin of a part of the body, a pair of input electrodes for feeding a measuring alternating current to the part of the body and a measuring pair of electrodes for measuring the voltage at the electrodes of the measuring pair of electrodes, comprising a current source providing the measuring 10 alternating current, a converter for the transformation of the measuring voltage into a bio-impedance signal, being a measure of the bio-impedance of the part of the body, and means for the generation of signals which form a measure 15 for further variables with the aid of which said parameter can be determined using the calculating model, said signals encompassing a signal forming a measure for the time derivative of the bio-impedance signal.

Such an apparatus is known from the international 20 patent application WO-A-90/00367. This known apparatus is used to determine a number of biological parameters of the thorax of a patient by means of a bio-impedance measurement. However, the measurement is rather inaccurate because the fluid distribution in the patient is not taken 25 into account. With the known apparatus there is also a local bio-impedance measurement; this is used for the determination of an average arterial pressure.

It is the object of the invention to apply the measuring results becoming available when employing this 30 apparatus in such a way that the biological parameter can be determined more accurately.

To this end the apparatus of the invention is characterized in that the current source has a minimal radiation configuration and is suitable for generating a 35 measuring current having a constant amplitude on at least

two frequencies, a low frequency and a high frequency, in a frequency range of up to about 2000 kHz. This provides independent measurements and reduces interfering effects caused by electromagnetic radiation at high frequencies.

5 The biological parameters that can be determined by means of the apparatus according to the invention include preferably the measuring of a circulatory parameter and more preferably the stroke volume of a heart. Further, the so-called cardiac output which is derived from the stroke
10 volume and the heart rhythm, the so-called cardiac index, the left ventricle ejection time, the right ventricle ejection time, the prejection period, the Heather index, the acceleration index, and venous occlusion plethysmography. These terms are known to the expert and
15 need no further explanation. Other biological parameters that may be determined by means of the apparatus are, for instance, the distribution between extracellular and intracellular bodily fluids and the distribution of fluid during a septic shock.

20 It is observed, that the application of several frequencies for the determination of a biological parameter is known as such.

In the article "Multiple frequency system for body composition measurement", Proc. of the Int. Conf. of the
25 IEEE Engineering in Medicine and Biology Society, Vol. 15, Oct. 1993, pp. 1020, 1021, currents of different frequencies are used for the measurement and determination of a body parameter. The maximum frequency is, however, only 100 kHz, and no measures are given for combatting
30 radiation problems. The publication is limited to the determination of changes in the bladder contents.

The article "Two-frequency impedance plethysmograph: real and imaginary parts", Med. & Biol. Engineering & Computing, 28 (1990) January, No. 1, pp. 38-
35 42, describes a multi-frequency measuring system for the analysis of fluid volume ratios in the thorax where two different frequencies are used having a maximum measuring frequency of only 110 kHz.

The article "Microprocessor-based system for measurement of electrical impedance during haemodialysis and in postoperative care", Med. & Biol. Engineering & Computing, 26 (1988) January, No. 1, pp. 75-80, describes a system for tetrapolar impedance plethysmography for the determination of fluid and the fluid volume ratios in the thorax. Three oscillators are used for this purpose, two of which operate on 2½ and 100 kHz respectively and a third has an oscillation frequency of 1 kHz to 1 MHz.

The US patent specification 4,870,578 describes an apparatus for the determination of the stroke volume of a heart by means of bio-impedance measurement. The apparatus according to this publication comprises means for sending a constant, high frequency current through the thorax of a person to be examined, as well as means for measuring a consequentially induced voltage over the thorax, from which signal the impedance of the particular thorax is derived. From this impedance the time derivative is determined, and a limited time portion of this time derivative subsequently serves as a measure for the stroke volume of the heart in the thorax.

US patent specification 5,309,917 discusses a further development of such a bio-impedance measuring system departing from the known methods of determination according to Kubicek and Sramek.

According to Kubicek the stroke volume of the heart is determined by the formula

$$SV = \rho \frac{L^2}{Z_0^2} \left(\frac{dZ}{dT} \right)_{\text{min}} \cdot VET$$

In this formula ρ is the specific resistance of the blood, L is the distance at which the electrodes are placed for measuring the voltage, Z_0 is the average thorax resistance and VET is the ventricular ejection time. The current source provides a current having a frequency of about 100 kHz.

An alternative form according to which the stroke volume is determined is provided by Sramek:

$$5 \quad SV = \frac{V_{EPT}}{Z_0} \cdot VET \left(\frac{dZ}{dt} \right)_{\min}$$

in which V_{EPT} is the volume of the thorax participating in the electric conduction. This volume depends on the height
10 and weight of the particular person.

The general formula for the stroke volume may be expressed as

$$15 \quad SV = \mu \cdot \eta \frac{VET \left(\frac{dZ}{dt} \right)_{\min}}{Z_0}$$

20 in which η is a personal form factor, and μ a corrective factor for oedema formation in the thorax.

According to US 5,309,917 a time frequency diagram is determined for the measured time derivative of the bio-impedance signal. The stroke volume of the heart is then
25 derived from this frequency diagram, while the stroke volume is assumed to be dependent on the time lapse between the first frequency signal in this distribution and the point in time when the time derivative of the bio-impedance signal reaches the maximum value.

30 A current source in a minimum radiation configuration in said frequency range up to about 2000 kHz is advantageously realized by giving it an electrically symmetrical configuration thus providing it with a galvanic separation in relation to the instrument earth.

35 Optimal separation of measurement results becoming available on the two different frequencies is obtained because the low frequency f_l is in the region of about 1-64 kHz and the high frequency f_h in the region of about 32-2000 kHz, such that in all cases f_l is smaller than f_h . By
40 choosing the measurement frequencies thus, the difference in sensitivity is optimal for both situations. The rela-

tively low frequency currents are transmitted mainly through the extracellular fluid, while the high frequency currents are also transmitted through the intracellular fluid. Fluid distribution may, for instance, be analyzed by means of the so-called Cole-Cole-model, which is based on a Nyquist analysis of a simple equivalent-circuit diagram of the thorax, based on a parallel circuit of a purely resistive component for the relatively low frequencies and for the high frequencies a series connection of a resistive and a capacitive component. Consequently, by applying the known formulas for the determination of the stroke volume and other biological parameters, different frequencies provide independent measurements for those parameters. These measurements provide information about the above-mentioned correction factor μ . With the aid of the measured impedance Z_0 , or through determination of the measured phase angle, φ , the ratio intracellular and extracellular fluid can be determined at different frequencies.

Preferably the current source is suitable for simultaneous generation of the two frequencies. This has the advantage that the time the patient has to be connected to the apparatus for measurement is shortened.

In addition it is desirable that means are provided for the determination of maximum phase shift between the measuring current and the measuring voltage as a function of the frequency. This allows the electric transfer function of the particular part of the body to be determined, with the angular frequency being the independent variable. This permits at the same time the determination of the ratio between intracellular and extracellular fluid; because this ratio is directly related to the frequency at which the phase angle is at a maximum. With healthy test persons this maximum phase angle is at about 9 to 10° at 70 kHz. This corresponds to an intracellular/extracellular fluid ratio of 3:7. With septic patients the maximum phase angle is, for instance, between 3 and 6°.

A preferred embodiment of the apparatus according to the invention is characterized in that said apparatus

comprises four pairs of electrodes, two pairs of electrodes being intended for taking a transversal bio-impedance measurement and two pairs of electrodes being intended for taking a local bio-impedance measurement. In
5 the case that the measurement is carried out on the thorax, the local bio-impedance measurement is to be carried out at a location removed from the heart.

The term "transversal measuring" used above, indicates a measurement in which the current runs substantially lengthways of the person to be examined.
10

The measure discussed just now allows a further correction to be carried out on the resulting measurements, due to the different test results of the cardiovascular system at a relatively low and a relatively
15 high frequency. With a local bio-impedance measurement a measurement check is thus obtained in which the interfering influence of the cardiovascular system is eliminated. In this way the local measurement produces a correction signal to compensate the transversal
20 measurement.

The apparatus is preferably provided with connecting means for connecting the current source and the transformer in series, in order to sequentially carry out the local bio-impedance measurement and the transversal
25 bio-impedance measurement. This limits the number of components comprising the apparatus, and by always employing the same system parts an optimally reproducible measurement is obtained.

In another embodiment the apparatus according to
30 the invention is characterized in that said apparatus comprises a current source or current sources suitable for the simultaneous generation of signals at two low frequencies and two high frequencies, so as to limit the inconvenience for a patient to be examined. These
35 frequencies all range from about 4 to 2000 kHz, with a first low frequency and a first high frequency being coupled to a first two pairs of electrodes to carry out the local bio-impedance measurement and the second low frequency and the second high frequency being coupled to

the second two pairs of electrodes to carry out the transversal bio-impedance measurement. In this way both measurements can be carried out simultaneously.

It is further desirable that the measurement amplifier or measurement amplifiers are configured electrically symmetrical and are provided with a galvanic separation in relation to the instrument earth. This increases the resistance to common mode interference signals.

Also, the input stage of the apparatus is inductively coupled, thereby reducing transmission of the interference signal residue.

The invention will now be further elucidated with reference to the drawing, in which

Fig. 1a represents schematically a first measuring arrangement of the apparatus according to the invention;

Fig. 1b represents schematically a second measuring arrangement of the apparatus according to the invention;

Fig. 2 shows an example of the progress of measuring signals perceived by the apparatus according to the invention;

Fig. 3a represents schematically the current source of the apparatus according to the invention;

Fig. 3b represents schematically a non-low-radiation current source according to the prior art;

Fig. 3c represents schematically a low-radiation current source according to the invention;

Fig. 4 represents schematically the input stage of the apparatus according to the invention;

Fig. 5 represents schematically an intra- and extracellular conduction, the so-called Cole-Cole model (5a), with corresponding vector diagram (5b) and Bode plots of amplitude (5c) and phase (5d); and

Fig. 6 shows an embodiment of the converters employed in the apparatus according to the invention.

Fig 1a shows a block diagram of an embodiment of the apparatus for carrying out simultaneous measurements on a patient 1. By means of current supply electrodes 2 and 3 current from a current source 7 is supplied to a patient 1. The voltage resulting from current passing

through the tissue of the test person 1 is measured by means of a pair of electrodes 4 and 5 which are connected with a differential amplifier 6. The electrodes 4 and 5 serve for the transversal measurement. Current input 5 electrodes 8 and 9 are locally placed on the patient 1 and are connected with current source 12. The resulting voltage over the tissue between said electrodes is measured by means of the electrodes 10 and 11 which are connected with differential amplifier 13. The electrodes 10 and 11 serve for the local measurement.

The output of the differential amplifier 6 is fed into a calculating element 14 providing an electric bio-impedance signal $Z_1(t)$ which is directly related to the bio-impedance of the thorax of the patient 1 as a function 15 of the time and a phase signal φ_1 which is directly related to the phase difference between the current supplied by means of a current source 7 and the voltage measured by electrodes 4 and 5. Similarly, the output of the differential amplifier 13 is supplied to the calculating element 20 15 which provides an electric bio-impedance signal $Z_2(t)$ which is directly related to the bio-impedance of a locally measured part of the body as a function of the time and a phase signal φ_2 which is directly related to the phase difference between the current supplied into said 25 part of the body and the resulting voltage over that part of the body as measured by means of the electrodes 10 and 11.

The electric bio-impedance signal $Z_1(t)$ and the phase signal φ_1 are fed into a processor 17 in order to 30 determine a parameter to be identified below. The frequency and possibly the amplitude of the current source 7 are preferably controlled by the processor 17. In order to carry out the necessary operations, the electrocardiogram (ECG) obtained at the output side of the differential 35 amplifier 6 or from a separate ECG amplifier (not shown), is fed into the processor 17. Similarly, the signals $Z_2(t)$ and φ_2 are fed into the processor 16 for the determination of the fluid distribution in the locally measured part of the body. The resulting parameters are then fed into the

processor 17 for the determination of correction factors in the operations carried out by processor 17. The above-mentioned ECG also serves for the improvement of accuracy. The output of processor 17 showing the desired parameters, 5 is connected to indicator 18 for display and registration purposes.

Fig. 1b shows the circuit suitable for sequential measurement on the patient 1. The functions of blocks 6, 7, 14, 17 and 18 have already been elucidated. The switch 10 19 is controlled by the processor 17 for carrying out sequential measuring on the thorax bio-impedance and measuring the local bio-impedance of a part of the body of patient 1. Fig. 1b shows clearly that in a first situation the current source 7 is connected with the electrodes 2 15 and 3, while the differential amplifier 6 is at the same time connected with the electrodes 4 and 5 by which measuring of the thorax bio-impedance can then take place. In the other situation said current source is connected with the electrodes 8 and 9, while said differential 20 amplifier 6 is connected with the electrodes 10 and 11 so that local measuring of the bio-impedance of the part of the body of the patient 1 can take place.

Fig. 2 shows a typical progress of a bio-impedance signal ΔZ , as measured with the differential amplifier 6 25 baseed on an excitation by current source 7. The progress of this signal is time-dependant in particular because of the pumping activity of the heart of the test person 1. The time derivative of the signal ΔZ , dZ/dt , is shown one row higher in Fig. 2. According to the prior art, when 30 determining the stroke volume of the heart, this is approximated by multiplying the minimum value of the time derivative $(dZ/dt)_{\min}$ by a time interval which is determined by the characteristic waveforms in the signal dZ/dt . In the field this time interval is indicated as 35 (left) ventricular ejection time (abbreviated (L)VET), and is dependent on a point in time at the beginning of a curve indicated by B and a point in time determined by the next maximum in the time derivative indicated by C. For

synchronization purposes the top row shows the electrocardiogram (ECG) of the test person 1.

In accordance with the invention, measuring errors ensuing due to over- or underweight of the test person 1 or due to measurements carried out under conditions where the normal moisture balance of the test person is upset, for instance with oedema formation, are prevented due to the fact that the current source 7 can generate an electric current having at least two frequencies. By processing the data from current source 7 in a calculating element 14, the measuring results becoming available from differential amplifier 6 are converted into a bio-impedance signal Z , while this element 14 also determines the phase difference φ between the current from source 7 and the voltage from amplifier 6. The current source 7 can generate a current having frequencies in the range of about 4 kHz to about 2000 kHz; if desired, the current source 7 can simultaneously generate currents having different frequencies. In a processor 17, the frequency-dependent measuring results for a particular thorax transfer model may be transformed into a current distribution factor which is dependent on the geometry of the test person 1. For this the moisture distribution according to the Cole-Cole-model may be used by means of which a current ratio between the intracellular fluid and the extracellular fluid can be determined. This current ratio corresponds to the current distribution over the cardiovascular system and the rest of the thorax. In a particular embodiment the current source 7 is suitable for the generation of a electric current having a frequency sweep of about 4 kHz to 2000 kHz, while the calculation element 14 is also suitable for the determination of the maximum phase angle dependent on the frequency. Based on this data the moisture distribution can be determined with the aid of a Bode analysis of the transfer model of the thorax by determining the maximum phase angle and possibly the frequency at which this occurs. Normally the maximum phase angle is about 9 to 10° at a frequency of 70 kHz.

Similarly, a local impedance measurement can be carried out by means of the electrode pairs 8, 9 and 10, 11. The measurement results becoming available through the measuring amplifier 13, together with data from the 5 current source 12 are fed into a calculation element 15, and from these a local impedance value and the phase angle between the current from the source 12 and the voltage from the differential amplifier 13 are determined. In a manner similar to the one described above, the measuring 10 data thus derived are further processed in a processor 16 in order to determine the current distribution over the cardiovascular system and the rest of the thorax. This measuring signal suffering no interference from the heart's pumping action, is subsequently also fed into the 15 processor 17 to compensate the measuring data obtained from the transversal measurement. The measuring data thus corrected may then be made available for reading via an indicator 18. If necessary, special operations may be carried out by feeding the ECG signal to the processors 20 16, 17.

Fig. 3a shows the block diagram of the current source. The current source comprises a floating part which is electrically insulated with respect to its housing. A pure sine form whose frequency is controlled by processor 25 17 is generated by means of the oscillator 212 and is inductively coupled to the floating part of the current source by means of the transformer 214. The output of said transformer is fed into a wideband amplifier 210 whose amplification is controlled by the processor 29. The 30 output of said amplifier is fed into a wideband capacity amplifier 211, being coupled at its output side via a transformer 215 to the current feed electrodes placed on the patient 1.

The transformer 215 comprises two analogous secondary windings connected with each other in such a way that a current i can be measured by means of determining the voltage over a precision resistor 27. The live cables 25 and 26 are protected in order to reduce the electromagnetic field generated by this cable. However,

this protection could cause a problem, because with the increased frequency an increased current resulting from the capacity of these cables, plays a role. However, in the embodiment shown employing secondary windings of

5 transformer 215 and precision resistor 27, only the current running through the patient is determined. The wideband amplifier 216 measures the voltage produced at the spot of said precision resistor 27, which data is fed into processor 29 in order to be compared with an

10 amplitude control signal coming, for instance, from processor 17 or from a reference present in the processor 29. The processor 29 emits a voltage V_c for the control of the amplification of amplifier 210. By the control loop thus realized, the amplitude of current i is directly

15 related to the amplitude control signal so that said current is stabilized. The amplitude control signal is preferably generated by processor 17. At the same time processor 29 transforms the voltage over resistor 27 into a reference signal f_r for the phase measurement. By

20 employing an optocoupler 213 this signal is transmitted galvanically separated.

As a rule, an electric apparatus is prone to the development of electromagnetic stray fields. The provision of a floating part which is electrically insulated from

25 the rest of the electronics, reduces these stray fields to a certain extent.

Fig. 3b shows a current source according to the prior art, from which can be seen that the amplitude of the parasitic current is determined by the measure of

30 parasitic capacity 217 and the insulation capacity 218. The parasitic capacity 217 is determined by the body surface of the patient 1. The diagram in Fig. 3c shows the symmetric arrangement according to the invention, as a result of which no voltage is generated over the

35 insulation capacity, with the result that the effective parasitic capacity is reduced.

Fig. 4 shows a block diagram of the differential amplifiers 6 and 13. Said amplifiers are divided into an electrically insulated part (floating part) comprising a

pair of amplifiers 35 consisting of a junction FET 50, 51 and a PNP-transistor 52, 53 arranged symmetrically. The emission resistor 36 and the decoupling capacity 37 form a time constant τ . The performance of the circuit can be divided into a frequency range below the cut-off frequency $f_c = \frac{1}{2} \pi \tau$ and the frequency range above f_c . It may be assumed that below f_c the effect of the transformer 31 becomes negligible as a result of which the circuit behaves like a differential amplifier whose outputs are formed by the emitters of the PNP transistors 52, 53. The signal present on these emitters is passed on via the insulation amplifier 33. For the frequencies well above f_c the circuit behaves like a differential source follower connected with the transformer 31. In this way the current input side serves as an amplifier for the electrocardiogram signal since this signal holds frequency to about 100 Hz, being well below f_c . Similarly, for frequencies above 1 kHz the circuit serves as input side impedance transformer for the bio-impedance measurement for the conduction of the high frequency signal measured at the location of the electrodes 4 and 5, to transformer 31. Said transformer conducts the signal over the galvanic separation to the amplifier 32 and realizes at the same time an impedance matching. The circuit shown with current source 30 in combination with the floating input, results in suppression of common mode signals at the location of the measuring electrodes.

Fig. 5 shows the determination of the frequency behaviour of the Cole-Cole model with the aid of Bode analysis. Fig. 5 shows the actual Cole-Cole model, the vector diagram of current and voltages and the amplitude and phase diagrams as a function of the frequency. The frequency transmission is provided by the formula

$$35 \quad P(j\omega) = \frac{\frac{\tau_2}{\tau_1} \cdot (1+j\omega\tau_1)}{1+j\omega\tau_2} \quad (4)$$

The maximum phase angle φ_{\max} depends on the ratio τ_2/τ_1 and occurs at frequency ω_m .

5

$$\varphi_{\max} = 90^\circ - 2 \tan^{-1} \sqrt{\frac{\tau_2}{\tau_1}} \quad (5)$$

This results in:

10

$$\frac{\tau_2}{\tau_1} = \left(\tan \frac{(90^\circ - \varphi_{\max})}{2} \right)^2 \quad (6)$$

15

Since $\tau_1 = (R_e + R_i) C_m$ en $\tau_2 = R_i C_m$ it follows that:

20

$$\frac{\tau_2}{\tau_1} = \frac{R_i}{R_e + R_i} = \frac{R_e}{R_i} = \frac{\tau_1}{\tau_2} - 1 \quad (7)$$

The equations (5) and (6) can be used for the determination of the intra- and extracellular moisture distribution.

25

Fig. 6 shows a block diagram of a typical embodiment of the transformers 14 and 15. The signal from the amplifier 32 (see Fig. 4) is fed into a device 40 passing the signal to a demodulator formed by the amplifiers 42, 43 and 44, and a carrier regeneration oscillator 41 based on a phase-locked loop. Said oscillator adapts its frequency dependent on the signal received from device 40 such that no phase shift ensues. The output of oscillator 41 is used for the synchronized connection between the outputs of the amplifiers 42 and 43 in order to obtain complete rectification of the signal at the input of said amplifiers. Further, the output of the oscillator 41 is fed into a phase detector 46 for measuring the phase difference between the signal input of device 40 and a reference signal REF obtained from the optocoupler 28 (see Fig. 3) which depends directly on the current passing through the electrodes 2 and 3. The output of the detector 46 is fed through a low-pass filter 47, which low-pass filter 47 in itself is known, in order to obtain a signal which is directly related to the phase difference between the current input provided by current

40

45

source 7, 12 and the voltage measured by means of the differential amplifier 6, 13. The bio-impedance signal $Z(t)$ is obtained by feeding the output from amplifier 44 through a low-pass filter 45, which low-pass filter 45 in
5 itself is known.

CLAIMS

1. An apparatus for the in-vivo non-invasive measurement of a biological parameter concerning a bodily fluid of a person or animal according to a calculating model, wherein the apparatus is provided with at least two pairs of electrodes to be placed on the skin of a part of the body, a pair of input electrodes for feeding a measuring alternating current to the part of the body and a measuring pair of electrodes for measuring the voltage at the electrodes of the measuring pair of electrodes, comprising a current source providing the measuring alternating current, a converter for the transformation of the measuring voltage into a bio-impedance signal, being a measure of the bio-impedance of the part of the body, and means for the generation of signals which form a measure for further variables, with the aid of which said parameter can be determined using the calculating model, said signals encompassing a signal forming a measure for the time derivative of the bio-impedance signal, characterized in that the current source (7, 12) has a minimal radiation configuration and is suitable for generating a measuring current having a constant amplitude on at least two frequencies, a low frequency and a high frequency, in a frequency range of up to about 2000 kHz.

2. An apparatus according to claim 1, characterized in that the parameter is a circulatory parameter of the heart.

3. An apparatus according to claim 1 or 2, characterized in that the parameter is the stroke volume of the heart.

4. An apparatus according to any one of the preceding claims, characterized in that the current source or current sources (7, 12) are electrically symmetrical configurated and galvanically separated in relation to the instrument earth.

5. An apparatus according to any one of the preceding claims, characterized in that the low frequency

f_1 is in the region of about 1-64 kHz and the high frequency f_h in the region of about 32-2000 kHz, such that in all cases f_1 is smaller than f_h .

6. An apparatus according to any of the claims 1-5,
5 characterized in that the current source (7, 12) is suitable for simultaneous generation of the two frequencies.

7. An apparatus according to any of the claims 1-6, characterized in that said apparatus is provided with four pairs of electrodes (2, 3; 4, 5; 8, 9; 10, 11), two pairs
10 of which serve as input electrode pair (2, 3) and a measuring electrode pair (4, 5) for taking a transversal bio-impedance measurement at a low and a high frequency and two more pairs which serve as an input electrode pair (8, 9) and a measuring electrode pair (10, 11) for taking
15 a local bio-impedance measurement at a low and a high frequency.

8. An apparatus according to claim 7, characterized in that said apparatus is provided with connecting means (19) for connecting in series the current source (7) and
20 the transformer (6, 14), in order to carry out the local bio-impedance measurement and the transversal bio-impedance measurement in sequence.

9. An apparatus according to claim 7, characterized in that said apparatus comprises a current source or current sources (7, 12) suitable for the simultaneous generation of signals at two low frequencies and two high frequencies.

10. An apparatus according to any one of the preceding claims, characterized in that means (14, 15) are
30 provided for the determination of maximum phase shift between the measuring current and the measuring voltage as a function of the frequency.

11. An apparatus according to any one of the preceding claims, characterized in that the measurement
35 amplifier (6) for the amplification of the measuring voltage is configurated electrically symmetrical and is provided with a galvanic separation in relation to the instrument earth.

12. An apparatus according to claim 11, characterized in that the measuring amplifier (6) is provided with a galvanic separation (31) from a test person (1) who is to be coupled to the apparatus.

1/7

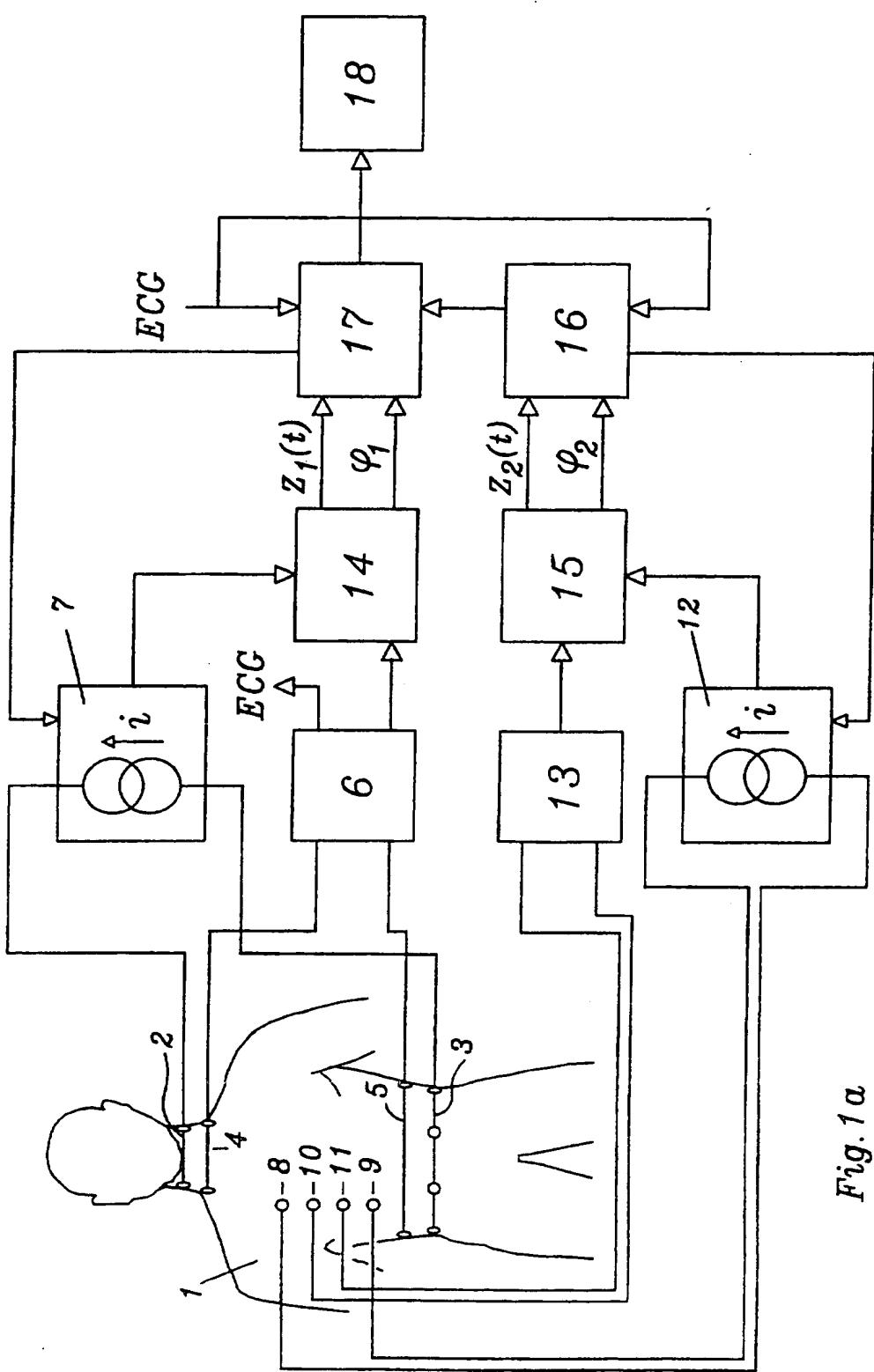


Fig. 1a

2/7

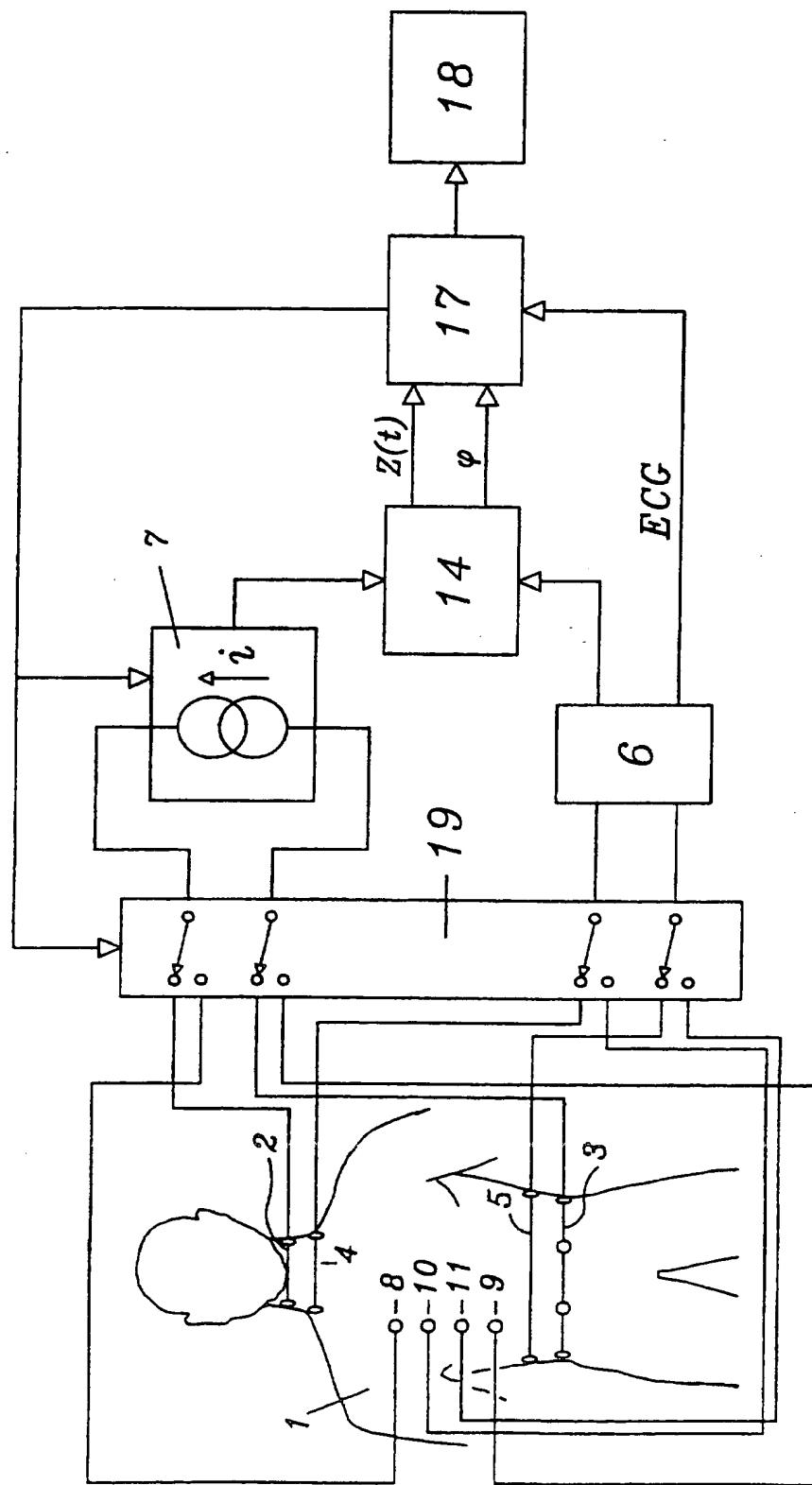


Fig. 1b

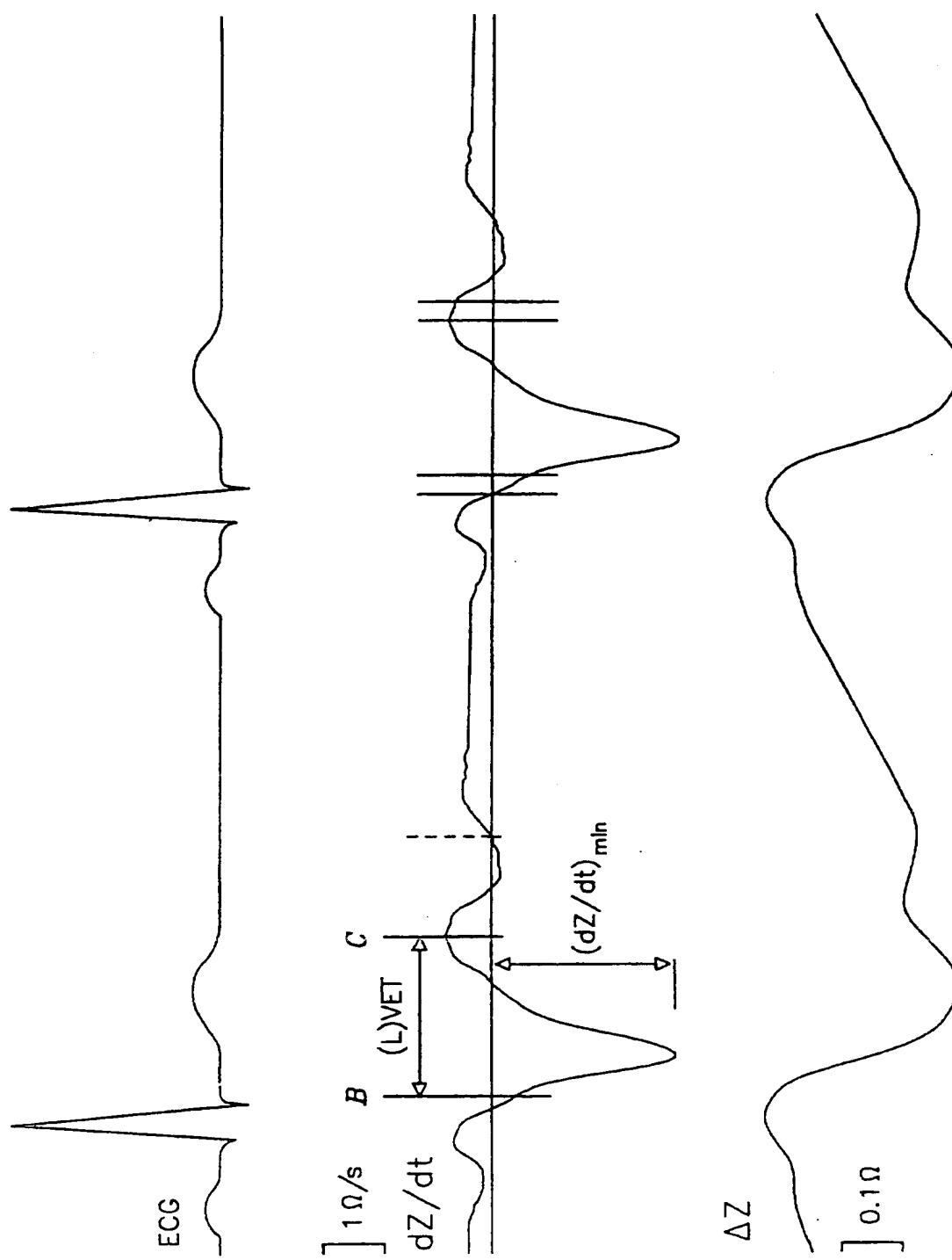


Fig. 2

4/7

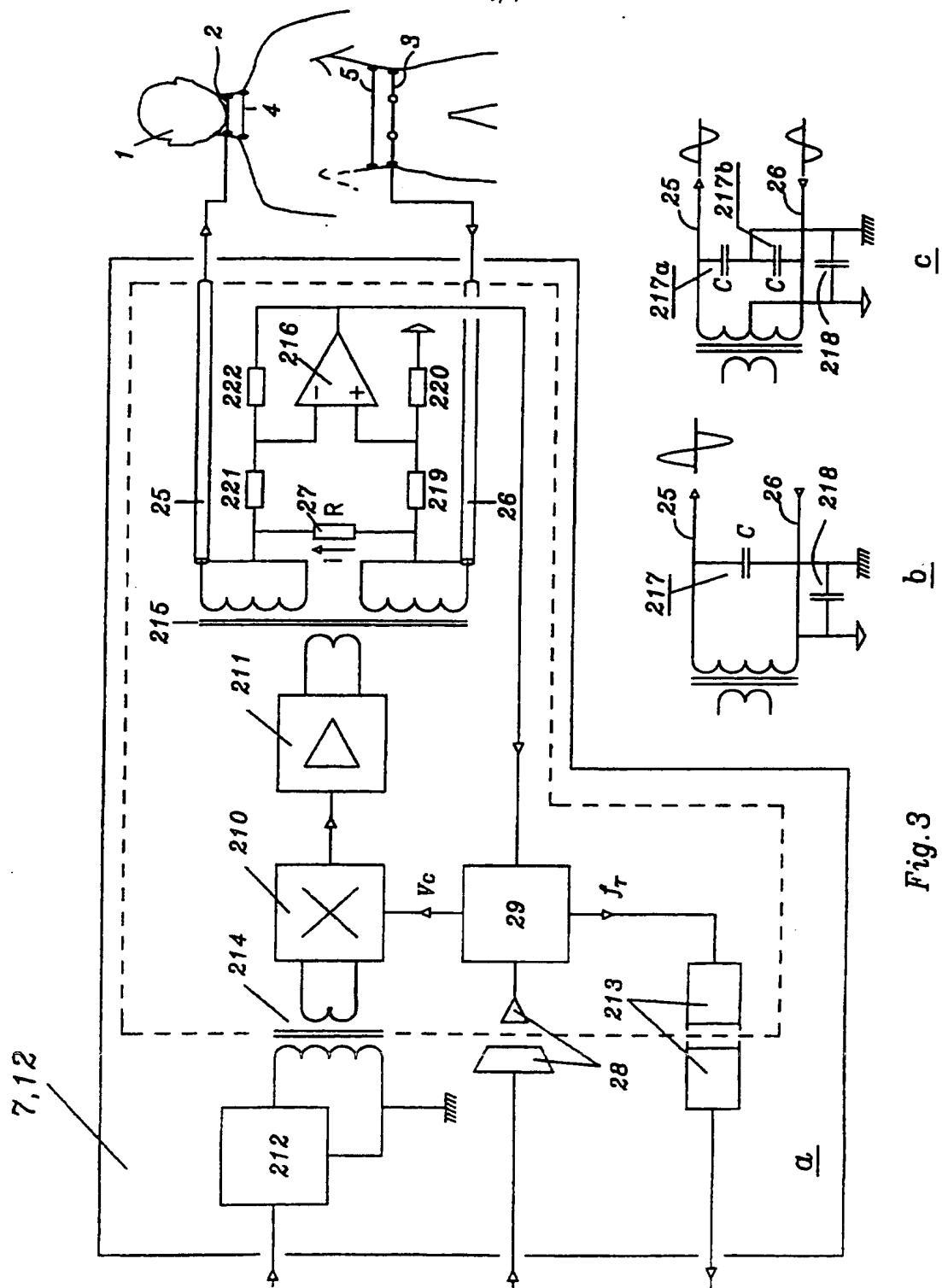


Fig. 3

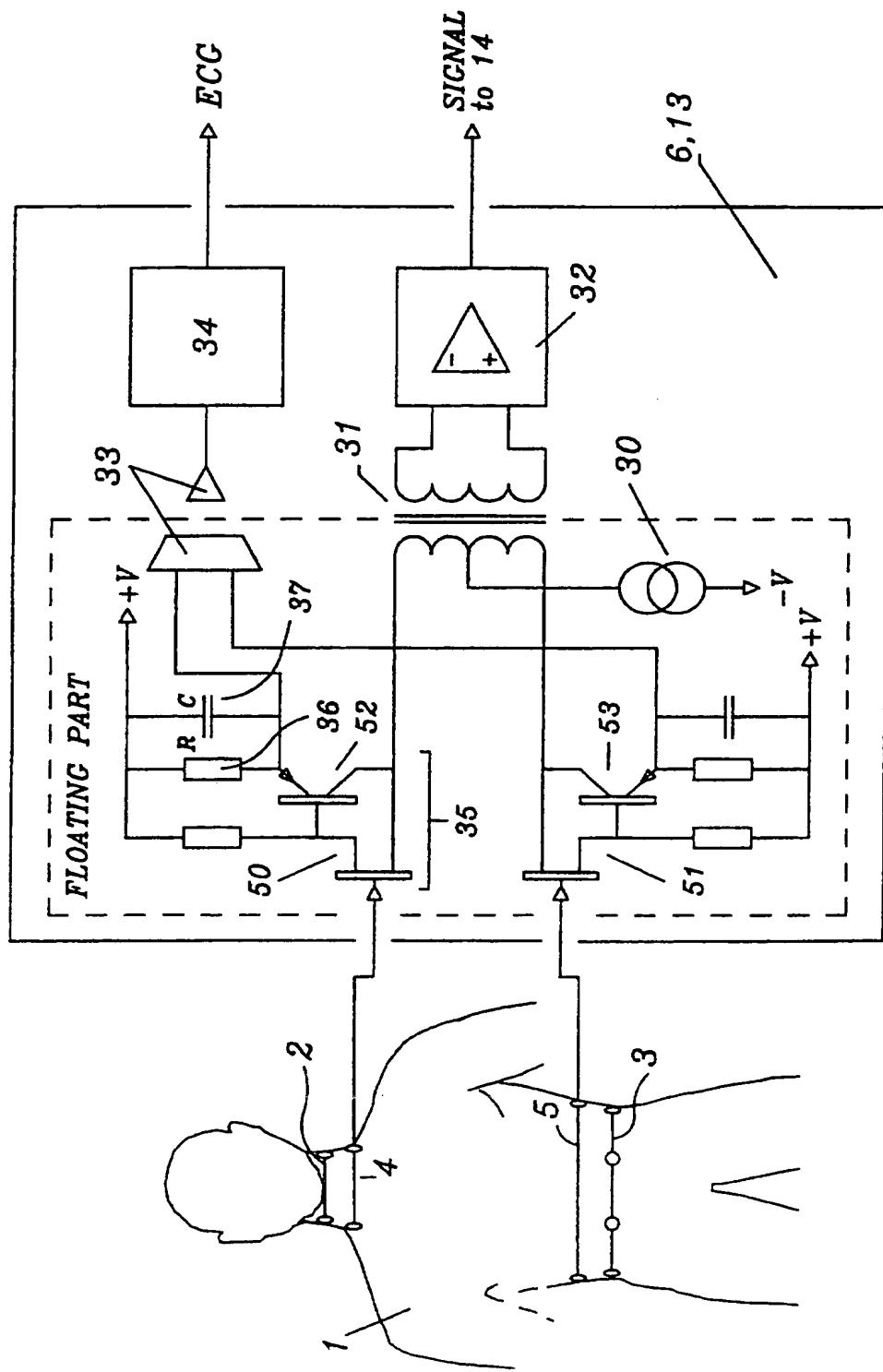


Fig. 4

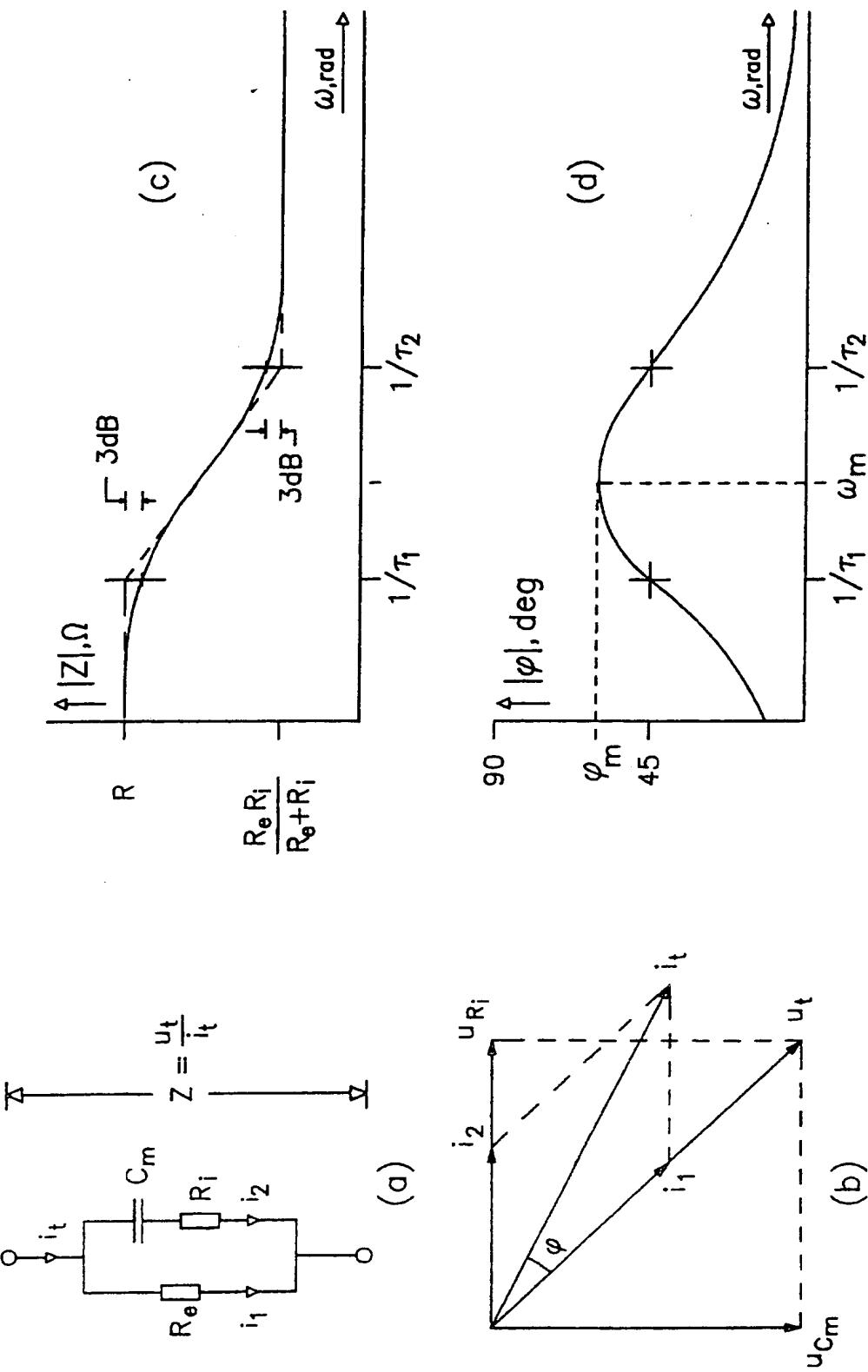


Fig. 5

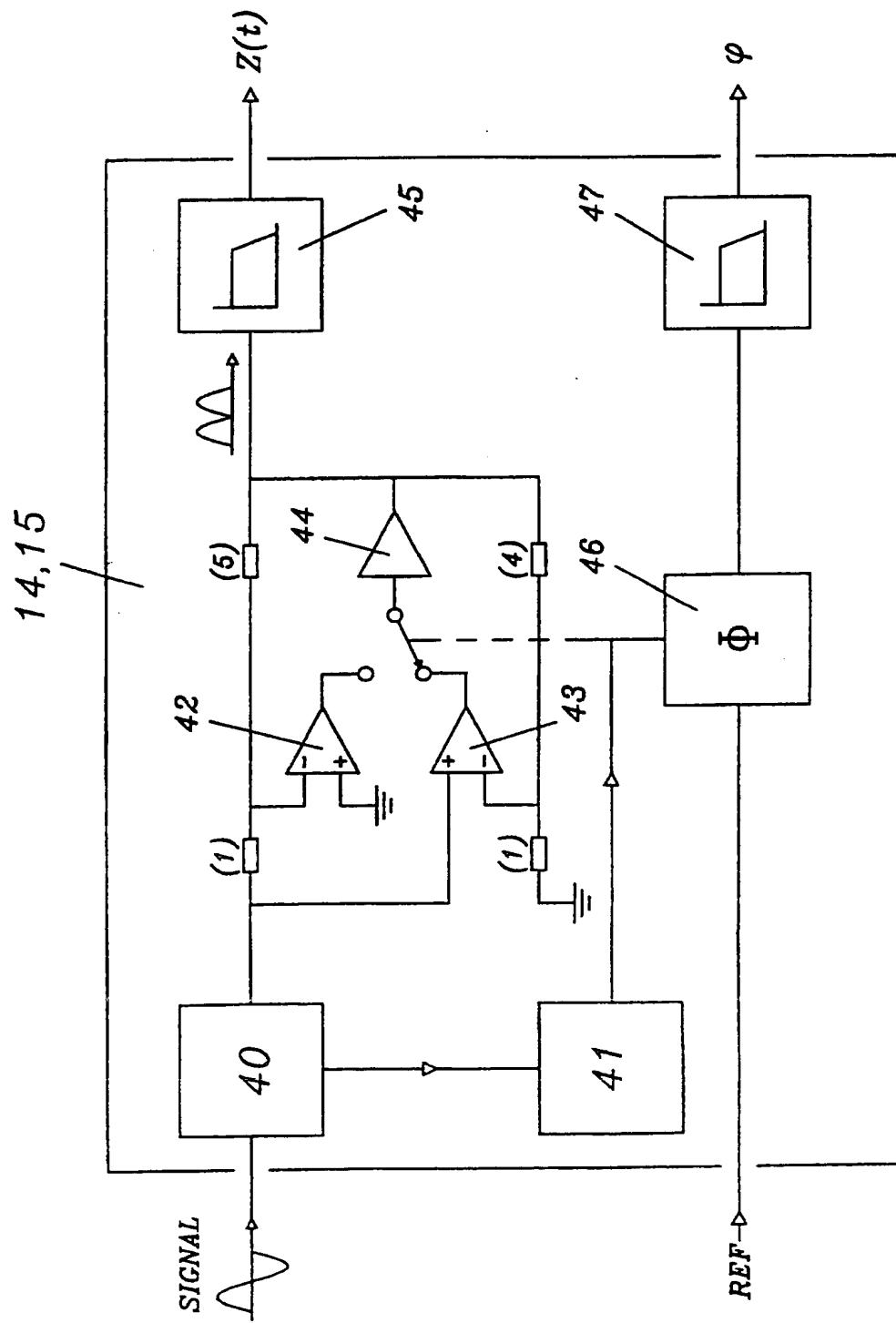


Fig. 6

PCT

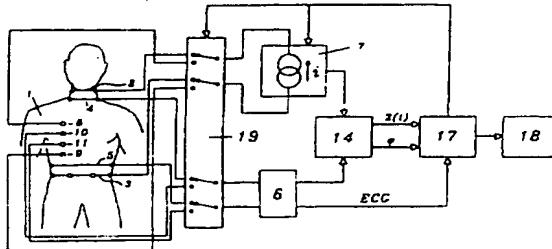
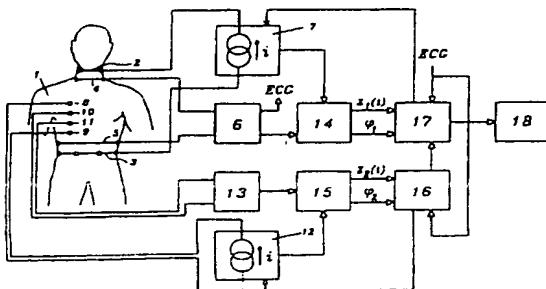
WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61B 5/05	A3	(11) International Publication Number: WO 97/11638 (43) International Publication Date: 3 April 1997 (03.04.97)
(21) International Application Number: PCT/NL96/00374		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 25 September 1996 (25.09.96)		
(30) Priority Data: 1001282 26 September 1995 (26.09.95) NL		
(71) Applicant (<i>for all designated States except US</i>): A.J. VAN LIEBERGEN HOLDING B.V. [NL/NL]; Rietspinner 11, NL-3831 DP Leusden (NL).		
(72) Inventors; and		Published
(73) Inventors/Applicants (<i>for US only</i>): HEETHAAR, Robert, Martin [NL/NL]; Willem Alexanderweg 44, NL-3945 CK Cothen (NL). GOOVAERTS, Hendrik, Gebhard [NL/NL]; Bruinjoost 15, NL-1241 HN Kortenhoef (NL).		<i>With international search report. In English translation (filed in Dutch).</i>
(74) Agent: VAN BREDA, Jacques; Octrooibureau Los en Stigter B.V., Weteringschans 96, NL-1017 XS Amsterdam (NL).		(88) Date of publication of the international search report: 29 May 1997 (29.05.97)

(54) Title: APPARATUS FOR THE IN-VIVO NON-INVASIVE MEASUREMENT OF A BIOLOGICAL PARAMETER CONCERNING A BODILY FLUID OF A PERSON OR ANIMAL



(57) Abstract

The invention relates to an apparatus for the in vivo non-invasive measurement of a biological parameter concerning a bodily fluid of a person or animal in accordance with a calculation model, wherein the apparatus is provided with connections for at least two pairs of electrodes (2-5, 8-11) to be placed on the skin of a part of the body, a pair of input electrodes (2, 3, 8, 9) for feeding a measuring alternating current to the part of the body and a measuring pair of electrodes (4, 5, 10, 11) for measuring the voltage at the measuring pair of electrodes, comprising a current source (7, 12) providing the measuring alternating current, a transformer (31) for the transformation of the measuring voltage into a bio-impedance signal, being a measure of the bio-impedance of the part of the body, and means for the generation of signals which form a measure for further parameters to be determined with the aid of the calculating model, said signals encompassing a signal forming a measure for the time derivative of the bio-impedance signal. The current source (7, 12) has a minimal radiation configuration and is suitable for generating a measuring current having a constant amplitude on at least two frequencies, a low frequency and a high frequency, in a frequency range of up to about 2000 kHz.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

INTERNATIONAL SEARCH REPORT

International Application No
PCT/NL 96/00374

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61B5/05

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 90 00367 A (BOMED MEDICAL MANUFACTURING, LTD.) 25 January 1990 see page 22, line 1 - page 26, line 35 see page 43, line 5 - page 44, line 28 see figures 4,7,9-12 ---	1-3,7
A	PROCEEDINGS OF THE ANNUAL INTERNATIONAL CONFERENCE OF THE IEEE ENGINEERING IN MEDICINE AND BIOLOGY SOCIETY, vol. 2, no. 2, October 1993, US, pages 1020-1021, XP000436991 EZENWA ET AL.: "Multiple frequency system for body composition measurement" see the whole document ---	1,2,5 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- 'A' document defining the general state of the art which is not considered to be of particular relevance
- 'E' earlier document but published on or after the international filing date
- 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- 'O' document referring to an oral disclosure, use, exhibition or other means
- 'P' document published prior to the international filing date but later than the priority date claimed

- 'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- 'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- 'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- '&' document member of the same patent family

1

Date of the actual completion of the international search Date of mailing of the international search report

11 March 1997

19.03.97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentdaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Chen, A

INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/NL 96/00374

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 575 984 A (TSOGLIN ET AL.) 29 December 1993 see page 6, line 37 - page 8, line 58 see page 10, line 2 - line 26 see page 11, line 35 - line 58 see figures 1A-2A,4 ---	1-4
A	MEDICAL & BIOLOGICAL ENGINEERING & COMPUTING, vol. 28, no. 1, January 1990, STEVENAGE, UK, pages 38-42, XP000297218 LOZANO ET AL.: "Two-frequency impedance plethysmograph: real and imaginary parts" see page 38, left-hand column, line 1 - page 41, left-hand column, line 14 see page 41, left-hand column, line 57 - page 42, left-hand column, line 32 see figures ---	1,2,4,5, 11
A	MEDICAL & BIOLOGICAL ENGINEERIN & COMPUTING, vol. 26, no. 1, January 1988, STEVENAGE, UK, pages 75-80, XP002004975 GOOVAERTS ET AL.: "Microprocessor-based system for measurement of electrical impedances during haemodialysis and in postoperative care" see page 75, left-hand column, line 1 - page 77, right-hand column, line 5 see figures 1,3 -----	1,2,5,7, 11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/NL 96/00374

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9000367 A	25-01-90	US	5103828 A	14-04-92
EP 575984 A	29-12-93	IL	102300 A	23-07-96
		JP	7031604 A	03-02-95
		US	5469859 A	28-11-95